

HFA 305

MAY 30 2001

Date of Approval: \_\_\_\_\_

## **FREEDOM OF INFORMATION SUMMARY**

### **ORIGINAL NEW ANIMAL DRUG APPLICATION**

**ANADA 200-302**

Iverhart<sup>TM</sup> Plus Flavored Chewables  
(ivermectin and pyrantel pamoate) Flavored Tablets

For the prevention of canine heartworm (*Dirofilaria immitis*) disease and  
for the treatment and control of adult *Toxocara canis*, *Toxascaris*  
*leonina*, *Ancylostoma caninum*, *Uncinaria stenocephala*, and  
*Ancylostoma braziliense*.

Sponsored by:

Blue Ridge Pharmaceuticals, Inc.,  
A Subsidiary of Idexx Laboratories, Inc.  
4249 Piedmont Parkway  
Greensboro, North Carolina 27410

ANADA 200-302

FOIS-1

## FREEDOM OF INFORMATION SUMMARY

### 1. GENERAL INFORMATION:

ANADA: 200-302

Sponsor: Blue Ridge Pharmaceuticals, Inc.  
4249-105 Piedmont Parkway  
Greensboro, NC 27410

Generic Names: Ivermectin and Pyrantel (as pamoate salt)

Trade Name: Iverhart™ Plus

Dosage Form: Flavored, Chewable Tablets

How Supplied: Three dosage strengths are available for dogs of different weight classes. Each tablet size is packaged in blisters (6 tablets per card).

How Dispensed: Rx

Amount of Active Ingredients: Small tablet contains 68 mcg of ivermectin and 57 mg pyrantel as pyrantel pamoate; medium tablet contains 136 mcg of ivermectin and 114 mg pyrantel as pyrantel pamoate; large tablet contains 272 mcg of ivermectin and 227 mg pyrantel as pyrantel pamoate.

Route of Administration: Oral

Species: Canine

Labeled Dosage: A minimum of 6 mcg of ivermectin and 5 mg of pyrantel pamoate/kg of body weight at monthly intervals.

Indications for Use: Iverhart Plus is indicated for the prevention of canine heartworm (*Dirofilaria immitis*) disease and for the treatment and control of adult *Toxocara canis*, *Toxascaris leonina*, *Ancylostoma caninum*, *Uncinaria stenocephala*, and *Ancylostoma braziliense*.

Pioneer Product: Heartgard® Plus, NADA 140-971, Merial Ltd.

### 2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Restoration Act (53 FR 50460, December 15, 1988, First GADPTRA Policy Letter) an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). Under the Act, approval of a generic product requires a demonstration of bioequivalence to the pioneer product. Bioequivalence of the generic and pioneer products can be demonstrated by a clinical end-point study (61 FR 26182, May 24, 1996; Bioequivalence Guidance). The ANADA relies on the target animal safety and drug effectiveness data in the pioneer's New Animal Drug Application (NADA).

***Effectiveness:***

The effectiveness of ivermectin has been established by data contained in approved NADA 140-971, sponsored by Merial. The following studies establish the bioequivalence of the generic product, Iverhart Plus to the pioneer product, Heartgard Plus.

**Clinical Endpoint Bioequivalence for Canine Heartworm Disease Prevention**

The ivermectin portion of this ivermectin/pyrantel pamoate combination is known to provide the efficacy for the claim of the prevention of heartworm disease in dogs. The following study was conducted to determine the clinical endpoint bioequivalence of the two products, Iverhart Plus and Heartgard Plus for the claim of heartworm prevention in dogs. Blood-level bioequivalence studies were not required for this approval because blood levels of ivermectin at the approved dose in dogs are too low for accurate measurement throughout the pharmacokinetic profile of the drug.

Testing Facility: TRS Labs, Inc.  
295 Research Drive  
Athens, GA 30605

Investigator: Dr. John W. McCall

Objective: The objective of this study was to compare the clinical endpoint bioequivalence of Blue Ridge Pharmaceuticals' Iverhart Plus (ivermectin/pyrantel pamoate) to that of Merial's Heartgard Plus (ivermectin/pyrantel pamoate) for heartworm (*Dirofilaria immitis*) prevention in dogs. Thirty-six beagle dogs (18 males and 18 females), ranging between 6.3 and 8.8 months of age and weighing between 18.5 to 30.5 pounds, were obtained from a USDA licensed supplier. All dogs were inoculated subcutaneously with 50 *D. immitis* L3 larvae thirty days prior to the first treatment. All of the infective larvae were from the same source, of the same age, and handled in the same manner for this study. The dogs were stratified by weight and gender, and randomly assigned to one of three treatment groups (6 males and 6

females per group). Dogs receiving the generic product (Group 1) and the pioneer product (Group 2) were treated every thirty days, for a total of four treatments. The dogs received a minimum dose of 6 mcg ivermectin and 5 mg pyrantel pamoate/kg of body weight. The negative control group (Group 3) received no treatment. Masking was accomplished by separation of function. All individuals responsible for making study observations, including worm counts, were masked to the treatment groups. All dogs were necropsied 119 days post-inoculation. The heart and lungs of each dog were removed and carefully examined to collect and count all *D. immitis* adults or macroscopic larvae.

Percent efficacy was calculated using the following formula:

$$\frac{\text{Mean \# of Parasites in control dogs} - \text{mean \# of parasites in treated dogs}}{\text{Mean \# of parasites in control dogs}} \times 100 = \% \text{ efficacy}$$

**Results and Conclusions:** The worm counts for both treated groups (Iverhart Plus and Heartgard Plus) were 0 and the mean worm count for the negative control group was 24, with all control animals having heartworm infections. Thus, the reference product and the pioneer product were considered bioequivalent with efficacies of 100%, and no statistical analysis was conducted. Based on the results of this clinical end-point bioequivalency study, Blue Ridge Pharmaceuticals' Iverhart Plus is bioequivalent to Merial's Heartgard Plus for the prevention of heartworms in dogs.

#### **Clinical Endpoint Bioequivalence for Gastrointestinal Nematodes.**

The effective treatment of the canine gastrointestinal nematodes, for which this combination of drugs, in this dosage form, is approved is provided by the pyrantel pamoate portion of the ivermectin/pyrantel pamoate combination. Clinical data has demonstrated that *Toxocara canis*, the canine roundworm, is the most resistant to the effects of pyrantel pamoate, of those parasites, for which the pioneer product is approved, therefore, demonstration of clinical endpoint bioequivalence for this parasite is sufficient proof of efficacy for all the gastrointestinal nematode parasites found on the Iverhart Plus label.

Blood-level bioequivalence studies were not required for this approval because pyrantel pamoate is poorly absorbed from the G.I. Tract, and the systemic absorption of the drug is not necessary for the desired clinical effect. In the case of clinical endpoint anthelmintic studies, if the generic and pioneer products are both  $\geq 90\%$  efficacious, and there is a statistically significant difference in the worm burdens of the treated groups as compared to the controls, then bioequivalence is established.

Two studies were conducted to demonstrate the clinical endpoint bioequivalence of Heartgard Plus and Iverhart Plus for the treatment of adult roundworms (*Toxocara canis*) in dogs. Both studies were conducted by the same investigator, at the same

facility, with the same objectives, and the same protocol design, but on different dates.

Testing Facility: CHK-R&D  
17190 Polk Road  
Stanwood, MI 49346

Investigator: Dr. Dwight Bowman

Objective: The objective of this study was to compare clinical endpoint bioequivalence of Blue Ridge Pharmaceuticals' Iverhart Plus (ivermectin/pyrantel pamoate) to that of Merial's Heartgard Plus (ivermectin/pyrantel pamoate) for the treatment of adult roundworms (*Toxocara canis*) in dogs.

Design: Thirty-six beagle dogs (18 males and 18 females) were obtained from a USDA licensed supplier. At inoculation, the dogs were 8 weeks of age and weighed between 4.55 and 8.05 pounds. All 36 dogs were inoculated orally with 300 embryonated *T. canis* eggs with the goal of obtaining 30 dogs positive for *T. canis* to include in the treatment groups. The 30 dogs (15 females, 15 males) with the highest mean egg per gram counts (EPGs) were stratified by EPGs within gender, and randomly assigned to one of three treatment groups (5 males and 5 females per group). Dogs receiving the generic product (Group 1) and the pioneer product (Group 2) were treated once at 49 days post-inoculation. The dogs received a minimum dose of 6 mcg ivermectin and 5 mg pyrantel pamoate/kg of body weight. The negative control group (Group 3) received no treatment. Masking was accomplished by separation of function. All individuals responsible for making study observations, including worm counts, were masked to the treatment groups. All dogs were necropsied 56 days post-inoculation. The gastrointestinal tract of each dog was removed and carefully examined to collect all *T. canis* worms. Recovered worms were counted, sexed, and preserved in 10% buffered formalin for retention. Percent efficacy was calculated using the geometric means of the log transformed data.

- Study One Results and Conclusions: The mean worm counts for the Iverhart Plus and Heartgard Plus groups were 4.6 and 1.0, respectively. The mean worm count for the negative control group was 27.5. Based on the geometric means of the log transformed worm counts, the efficacy was 93.07% for Iverhart Plus and 97.62% for Heartgard Plus. However, one dog receiving Iverhart Plus had a worm count of 35. There is no definitive explanation for the apparent lack of efficacy in this animal; however, it is possible that the animal vomited the medication unobserved, and was not adequately treated, or carried an excessive initial parasite burden. Based on the results of this clinical end-point bioequivalency study, Blue Ridge Pharmaceuticals' Iverhart Plus is bioequivalent to Merial's Heartgard Plus for the treatment of roundworm infections in dogs.

- **Study Two Results and Conclusions:** The mean worm counts for the Iverhart Plus and Heartgard Plus groups were 0.6 and 1.8, respectively. The mean worm count for the untreated control group was 23.5. Based on the mean worm counts, the % efficacy of Iverhart Plus was 97.45% and the % efficacy of Heartgard Plus was 92.34%. Based on the results of this clinical end-point bioequivalency study, Blue Ridge Pharmaceuticals' Iverhart Plus is bioequivalent to Merial's Heartgard Plus for the treatment of roundworms in dogs.

### **Palatability Study**

In addition to clinical end-point bioequivalence studies, a comparative palatability study was also performed to show that Iverhart Plus has similar palatability to Heartgard Plus.

#### **Investigators/Study Locations:**

Dr. Rodger Kleisch  
Forest Oaks Animal Clinic  
5310-H Liberty Road  
Greensboro, NC 27406

Dr. Julie Packard  
Bel-Aire Veterinary Hospital  
7712 Kenmont Road  
Greensboro, NC 27409

**Design:** A total of 69 client-owned dogs (45 spayed females, 1 female, 19 castrated males, 4 males) ranging in age from 1.1 to 12.7 years were enrolled in the study and included in the data analysis (70 dogs were initially enrolled, but one case was excluded from the analysis due to protocol non-compliance). A total of 20 breeds and mixed-breeds were represented and the body weights ranged from 7.8 to 97.2 pounds. One-half of the dogs received the generic tablet on day 1, followed by the pioneer tablet on day 2 and the other half received the pioneer tablet on day 1, followed by the generic tablet on day 2. The sequence of tablet administration was assigned using a randomization table generated using the SAS statistical package (Cary, NC). The owner recorded if the dog ate the tablet within 3 minutes.

**Results and Conclusions:** Iverhart Plus was palatable to 95.7% of the dogs and Heartgard Plus was palatable to 100% of the dogs. McNemar's test showed no statistical difference in palatability between the generic and pioneer product in palatability ( $p=0.0833$ ). Both Iverhart Plus and Heartgard Plus are palatable products.

### **3. HUMAN SAFETY:**

#### **Human Safety Relative to Food Consumption:**

None required as Iverhart Plus is intended for use only in dogs.

#### **Human Safety Relative to Possession, Handling, and Administration:**

Labeling contains adequate caution/warning statements.

#### 4. AGENCY CONCLUSIONS:

This is an Abbreviated New Animal Drug Application (ANADA) filed under section 512(b)(2) of the Federal, Food, Drug and Cosmetic (FFD&C) Act.

Safety and effectiveness for this generic animal drug, Iverhart Plus, were established by demonstration of clinical end-point bioequivalence to the pioneer product, Heartgard Plus, NADA 140-971.

This generic product and the pioneer product have identical labeling indications for use in dogs. The route and method of administration of the two drugs are identical. Both drugs are administered orally. The generic and pioneer products contain the same active ingredients.

This ANADA satisfies the requirements of section 512 of the Act and demonstrates that Iverhart™ Plus is safe and effective for its labeled indications, when used under the proposed conditions of use.

#### Attachments:

##### 1. Generic Labeling:

Package Insert

Blister Card Label for small, medium, and large tablets

Box Label for small, medium, and large tablets

Display Carton Label for small, medium, and large tablets

Bulk Carton Label for small, medium, and large tablets

Dispensing envelopes for bulk cards

Reminder Stickers

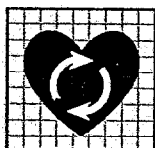
##### 2. Pioneer Labeling:

Package Insert

# IVERHART™ PLUS

(ivermectin/pyrantel)

*Flavored Chewables*



Store at controlled room temperature of 59°–86°F (15°–30°C).  
Protect product from light.

NADA 200-302, Approved by FDA.

Manufactured for: Virbac AH, Inc.  
Fort Worth, TX 76137, USA

For technical assistance or to report adverse drug reactions,  
please call 1-800-338-3659

IVERHART™ is a registered trademark.

Made in the USA.

Product Code XXXXXX-01

**virbac**

IVERHART™ PLUS  
(ivermectin/pyrantel)

(contains 6 Flavored Chewables)

up to 25 lbs

IVERHART™ PLUS

(ivermectin/pyrantel)

up to 25 lbs

(contains 6 Flavored Chewables)

IVERHART Plus IFC (Small Dogs up to 25 lbs.)



**IVERHART™ PLUS**

(ivermectin/pyrantel)

up to 25 lbs

**6**

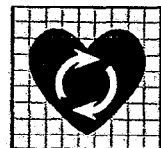
Warnings: Use product on or before its expiration date.  
Discard or return unused tablets

U.S.P.N.

**IVERHART™ PLUS**

(ivermectin/pyrantel)

*Flavored Chewables*



Each flavored chewable contains 68 mcg ivermectin  
and 57 mg pyrantel as pamoate salt.

**Keep this and all drugs out of the reach of children.**

*Recommended for dogs  
up to 25 lbs body weight*

*Contains 6 Flavored Chewables*



*Administer once a month to  
prevent heartworm disease  
and to treat and control  
ascarid and hookworm  
infections in dogs*

ANADA 200-302, Approved by FDA

**CAUTION:** Federal (U.S.A.) law restricts this drug to  
use by or on the order of a licensed veterinarian.

**virbac**

up to 25 lbs

Contains 6 Flavored Chewables

**IVERHART™ PLUS**  
(ivermectin/pyrantel)



Pantone 661 CV



Black

# IVERHART™ PLUS

(ivermectin/pyrantel)

## Flavored Chewables

Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

**INDICATIONS:** For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis*, *Toxascaris leonina*) and hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*).

**DOSAGE:** IVERHART™ PLUS (ivermectin/pyrantel) Flavored Chewables should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Flavored Chewable Per Month	Ivermectin Content	Pyrantel Content	Color Coding on Foil Backing and Carton
Up to 25 lbs	1	68 mcg	57 mg	blue
26 to 50 lbs	1	136 mcg	114 mg	green
51 to 100 lbs	1	272 mcg	227 mg	brown

IVERHART PLUS Flavored Chewables are recommended for dogs 6 weeks of age and older. For dogs over 100 lbs use the appropriate combination of these flavored chewables.

**ADMINISTRATION:** Remove only one flavored chewable at a time from the foil-backed blister card. Because most dogs find IVERHART PLUS Flavored Chewables palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food or placed in the back of the dog's mouth for forced swallowing.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

IVERHART PLUS Flavored Chewables should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of IVERHART PLUS Flavored Chewables must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the flavored chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with IVERHART PLUS Flavored Chewables and resumption of the recommended dosing regimen minimizes the opportunity for the development of adult heartworms.

Monthly treatment with IVERHART PLUS Flavored Chewables also provides effective treatment and control of ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*). Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

**EFFICACY:** IVERHART PLUS Flavored Chewables, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D. immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. IVERHART PLUS Flavored Chewables are also effective against canine ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*).

**ACCEPTABILITY:** In a trial in client-owned dogs, IVERHART PLUS Flavored Chewables were shown to be a palatable oral dosage form consumed at first offering by the majority of dogs.

**PRECAUTIONS:** All dogs should be tested for existing heartworm infection before starting treatment with IVERHART PLUS Flavored Chewables, which are not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with IVERHART PLUS Flavored Chewables.

While some microfilariae may be killed by the ivermectin in IVERHART PLUS Flavored Chewables at the recommended dose level, IVERHART PLUS Flavored Chewables are not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

**Keep this and all drugs out of the reach of children.** In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store at controlled room temperature of 59°–86°F (15°–30°C).

**Warnings:** Use product on or before its expiration date.

Discard or return unused tablets.

Protect product from light.

**ADVERSE REACTIONS:** In clinical trials with ivermectin, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of ivermectin: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

**SAFETY:** Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level of 6 mcg/kg) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. Ivermectin demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of ivermectin products in dogs, including Collies, when used as recommended.

Ivermectin has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with ivermectin/pyrantel in a heartworm disease preventive program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

**HOW SUPPLIED:** IVERHART PLUS Flavored Chewables are available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in a box of 6 tablets, packed 10 boxes per display box and in a bulk dispenser carton containing 20 cards of 6 tablets per card.

ANADA 200-302, Approved by FDA.

Manufactured for: Virbac AH, Inc.

Fort Worth, TX 76137, USA

For technical assistance or to report adverse drug reactions, please call 1-800-338-3659.

IVERHART is a registered trademark.

**virbac**

# IVERHART™ PLUS

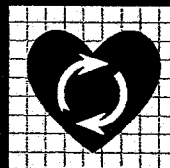
(ivermectin/pyrantel)

**Flavored Chewables**

**up to 25 lbs**

**Contains 10 Boxes, each containing  
a blister card of 6 Flavored Chewables**

Each flavored chewable contains 68 mcg ivermectin  
and 57 mg pyrantel as pamoate salt.



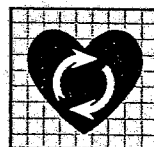
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(ivermectin/pyrantel)

*Flavored Chewables*

Each flavored chewable contains 68 mcg ivermectin  
and 57 mg pyrantel as pamoate salt.

**Keep this and all drugs out of the reach of children.**



***Recommended for dogs  
up to 25 lbs body weight***

*Contains 10 Boxes*



*Administer once a month to  
prevent heartworm disease  
and to treat and control  
ascarid and hookworm  
infections in dogs*

**ANADA 200-302, Approved by FDA**

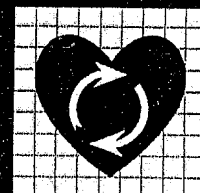
**CAUTION:** Federal (U.S.A.) law restricts this drug to  
use by or on the order of a licensed veterinarian.

***virbac***

# **IVERHART™ PLUS**

(ivermectin/pyrantel)

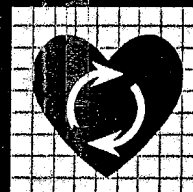
**Flavored Chewables**  
**up to 25 lbs**



# IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**  
**up to 25 lbs**



Store at controlled room temperature of 59°– 86°F (15°– 30°C).  
Protect product from light

ANADA 200-302, Approved by FDA.

Manufactured for: Virbac AH, Inc.  
Fort Worth, TX 76137, USA

For technical assistance or to report adverse drug  
reactions, please call 1-800-338-3659

IVERHART™ is a registered trademark.

Made in the USA.

Product Code XXXXXX-01

**Warnings: Use product on or before its expiration date.**  
**Discard or return unused tablets.**

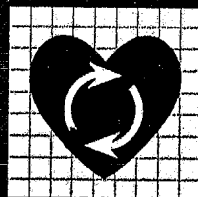
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**virbac**

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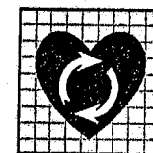
Flavored Chewables  
up to 25 lbs



## IVERHART™ PLUS

(ivermectin/pyrantel)

Flavored Chewables



Recommended for dogs up to 25 lbs body weight

Contains 10 Boxes



**CAUTION:** Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

*Administer once a month to prevent heartworm disease and to treat and control ascarid and hookworm infections in dogs*

**IVERHART™ PLUS**  
(ivermectin/pyrantel)  
26 to 50 lbs

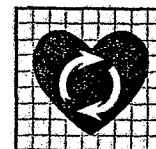
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Warnings: Use product on or before its expiration date.  
Discard or return unused tablets.

# IVERHART™ PLUS

(ivermectin/pyrantel)

## Flavored Chewables

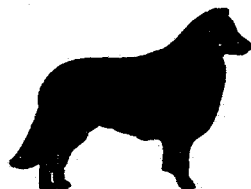


Each flavored chewable contains 136 mcg ivermectin  
and 114 mg pyrantel as pamoate salt.

**Keep this and all drugs out of the reach of children.**

*Recommended for dogs*  
**26 to 50 lbs body weight**

*Contains 6 Flavored Chewables*



*Administer once a month to  
prevent heartworm disease  
and to treat and control  
ascarid and hookworm  
infections in dogs*

ANADA 200-302, Approved by FDA  
**CAUTION:** Federal (U.S.A.) law restricts this drug to  
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**virbac**

26 to 50 lbs

Contains 6 Flavored Chewables

**IVERHART™ PLUS**  
(ivermectin/pyrantel)



Pantone 356 CV



Black

# IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**

**26 to 50 lbs**

**Contains 10 Boxes, each containing  
a blister card of 6 Flavored Chewables**

Each flavored chewable contains 136 mcg ivermectin  
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(ivermectin/pyrantel)

*Flavored Chewables*

Each flavored chewable contains 136 mcg ivermectin  
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*Contains 10 Boxes*



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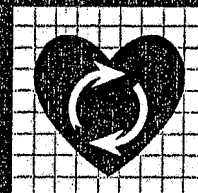


# IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**

**26 to 50 lbs**



Store at controlled room temperature of 59°– 86°F (15°– 30°C).

Protect product from light.

ANADA 200-302, Approved by FDA.

Manufactured for: Virbac AH, Inc.  
Fort Worth, TX 76137, USA

For technical assistance or to report adverse drug reactions, please call 1-800-338-3659.

IVERHART™ is a registered trademark.

Made in the USA.

Product Code XXXXXX-01

**Warnings: Use product on or before its expiration date.  
Discard or return unused tablets.**

Lot & Exp

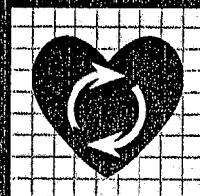
**virbac**

# IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**

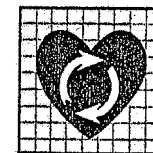
**26 to 50 lbs**



## IVERHART™ PLUS

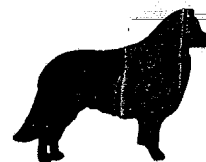
(ivermectin/pyrantel)

**Flavored Chewables**



*Recommended for dogs 26 to 50 lbs body weight*

*Contains 10 Boxes*



*Administer once a month to  
prevent heartworm disease and  
to treat and control ascarid and  
hookworm infections in dogs*

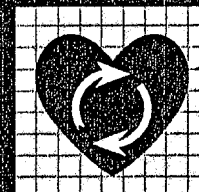
**CAUTION:** Federal (U.S.A.) law restricts this drug to  
use by or on the order of a licensed veterinarian.

# **IVERHART™ PLUS**

(ivermectin/pyrantel)

**Flavored Chewables**

**26 to 50 lbs**



**IVERHART™ PLUS**  
(ivermectin/pyrantel)  
51 to 100 lbs

**6**

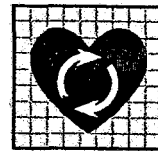
Warnings: Use product on or before its expiration date.  
Discard or return unused tablets

Lot & Exp.

# IVERHART™ PLUS

(ivermectin/pyrantel)

## Flavored Chewables



Each flavored chewable contains 272 mcg ivermectin  
and 227 mg pyrantel as pamoate salt.

**Keep this and all drugs out of the reach of children.**

*Recommended for dogs*

*51 to 100 lbs body weight*

*Contains 6 Flavored Chewables*



*Administer once a month to  
prevent heartworm disease  
and to treat and control  
ascarid and hookworm  
infections in dogs*

ANADA 200-302, Approved by FDA

CAUTION: Federal (U.S.A.) law restricts this drug to  
use by or on the order of a licensed veterinarian.

**virbac**



Pantone 4635 CV



Black

51 to 100 lbs

Contains 6 Flavored Chewables

**IVERHART™ PLUS**  
(ivermectin/pyrantel)

# IVERHART™ PLUS

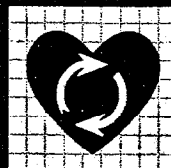
(ivermectin/pyrantel)

**Flavored Chewables**

**51 to 100 lbs**

**Contains 10 Boxes, each containing  
a blister card of 6 Flavored Chewables**

Each flavored chewable contains 272 mcg ivermectin  
and 227 mg pyrantel as pamoate salt.



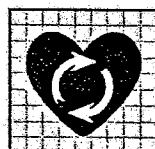
# IVERHART™ PLUS

(ivermectin/pyrantel)

*Flavored Chewables*

Each flavored chewable contains 272 mcg ivermectin  
and 227 mg pyrantel as pamoate salt.

**Keep this and all drugs out of the reach of children.**



***Recommended for dogs  
51 to 100 lbs body weight***

*Contains 10 Boxes*



*Administer once a month to  
prevent heartworm disease  
and to treat and control  
ascarid and hookworm  
infections in dogs*

**ANADA 200-302, Approved by FDA**  
**CAUTION:** Federal (U.S.A.) law restricts this drug to  
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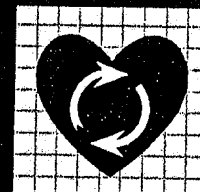
**virbac**

# IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**

**51 to 100 lbs**



Store at controlled room temperature of 59°– 86°F (15°– 30°C).

Protect product from light

ANADA 200-302, Approved by FDA.

Manufactured for: Virbac AH, Inc.  
Fort Worth, TX 76137, USA

For technical assistance or to report adverse drug reactions, please call 1-800-338-3659

IVERHART™ is a registered trademark.

Made in the USA.

Product Code XXXXX-01

**Warnings: Use product on or before its expiration date.  
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Lot & Exp

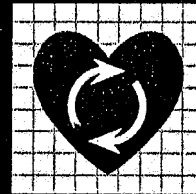
**virbac**

# IVERHART™ PLUS

(ivermectin/pyrantel)

Flavored Chewables

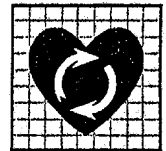
51 to 100 lbs



## IVERHART™ PLUS

(ivermectin/pyrantel)

Flavored Chewables



*Recommended for dogs 51 to 100 lbs body weight*

*Contains 10 Boxes*



**CAUTION:** Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

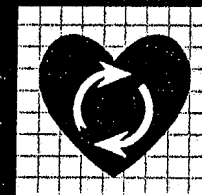
*Administer once a month to prevent heartworm disease and to treat and control ascarid and hookworm infections in dogs*

# **IVERHART™ PLUS**

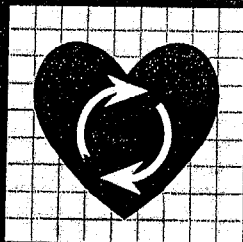
(ivermectin/pyrantel)

**Flavored Chewables**

**51 to 100 lbs**







# IVERHART™ PLUS

(ivermectin/pyrantel)

Flavored Chewables

up to 25 lbs

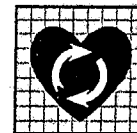
Contains 20 Blister Cards of  
6 Flavored Chewables each

Each flavored chewable contains 68 mcg ivermectin  
and 57 mg pyrantel as pamoate salt.

## IVERHART™ PLUS

(ivermectin/pyrantel)

Flavored Chewables



Each flavored chewable contains 68 mcg ivermectin  
and 57 mg pyrantel as pamoate salt.

Keep this and all drugs out of the reach of children.

*Recommended for dogs  
up to 25 lbs body weight*

Contains 20 Cards



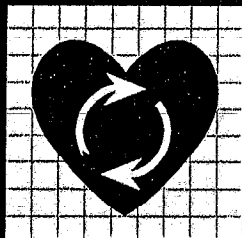
*Administer once a month to  
prevent heartworm disease  
and to treat and control  
ascarid and hookworm  
infections in dogs*

ANADA 200-302, Approved by FDA

CAUTION: Federal (U.S.A.) law restricts this drug to  
use by or on the order of a licensed veterinarian.

**virbac**

PUSH IN  
REMOVE THIS  
PANEL TO DISPENSE



# IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**

**up to 25 lbs**

**Contains 20 Blister Cards of  
6 Flavored Chewables each**

Each flavored chewable contains 68 mcg ivermectin  
and 57 mg pyrantel as pamoate salt.

## IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**

**up to 25 lbs**

Store at controlled room temperature of  
59°– 86°F (15°– 30°C).

Protect product from light

ANADA 200-302, Approved by FDA.

Manufactured for: Virbac AH, Inc.

Fort Worth, TX 76137, USA

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Made in the USA.

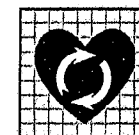
**Warnings:** Use product on or before its expiration date.

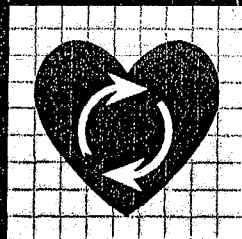
**Discard or return unused tablets.**

Lot & Exp

Product Code XXXXXX-01

**virbac**





# IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**

**26 to 50 lbs**

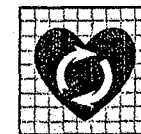
**Contains 20 Blister Cards of  
6 Flavored Chewables each**

Each flavored chewable contains 136 mcg ivermectin  
and 114 mg pyrantel as pamoate salt.

## IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**



*Each flavored chewable contains 136 mcg ivermectin  
and 114 mg pyrantel as pamoate salt.*

**Keep this and all drugs out of the reach of children.**

**Recommended for dogs  
26 to 50 lbs body weight**

**Contains 20 Cards**

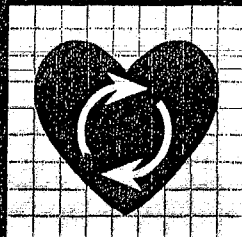


*Administer once a month to  
prevent heartworm disease  
and to treat and control  
ascarid and hookworm  
infections in dogs*

ANADA 200-302, Approved by FDA  
**CAUTION:** Federal (U.S.A.) law restricts this drug to  
use by or on the order of a licensed veterinarian.

**virbac**

**PUSH IN**  
REMOVE THIS  
PANEL TO DISPENSE



# IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**

**26 to 50 lbs**

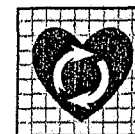
**Contains 20 Blister Cards of  
6 Flavored Chewables each**

Each flavored chewable contains 136 mcg ivermectin  
and 114 mg pyrantel as pamoate salt.

## IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**



**26 to 50 lbs**

Store at controlled room temperature of  
59°–86°F (15°–30°C).

Protect product from light

ANADA 200-302, Approved by FDA.

Manufactured for: Virbac AH, Inc.

Fort Worth, TX 76137, USA

For technical assistance or to report adverse drug  
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Made in the USA.

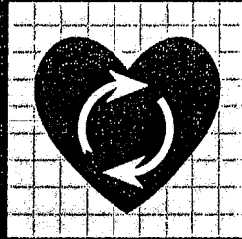
**Warnings: Use product on or before its expiration date.**

**Discard or return unused tablets.**

Lot & Exp

Product Code XXXXXX-01

**virbac**



# IVERHART™ PLUS

(ivermectin/pyrantel)

Flavored Chewables

51 to 100 lbs

Contains 20 Blister Cards of  
6 Flavored Chewables each

Each flavored chewable contains 272 mcg ivermectin  
and 227 mg pyrantel as pamoate salt.

# IVERHART™ PLUS

(ivermectin/pyrantel)

Flavored Chewables



Each flavored chewable contains 272 mcg ivermectin  
and 227 mg pyrantel as pamoate salt.

Keep this and all drugs out of the reach of children.

*Recommended for dogs*  
**51 to 100 lbs body weight**

**Contains 20 Cards**

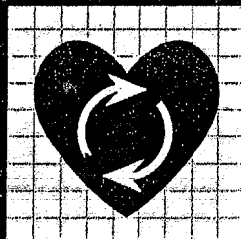


*Administer once a month to  
prevent heartworm disease  
and to treat and control  
ascarid and hookworm  
infections in dogs*

ANADA 200-302, Approved by FDA  
CAUTION: Federal (U.S.A.) law restricts this drug to  
use by or on the order of a licensed veterinarian.

**virbac**

PUSH IN  
REMOVE THIS  
PANEL TO DISPENSE



# IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**

**51 to 100 lbs**

**Contains 20 Blister Cards of  
6 Flavored Chewables each**

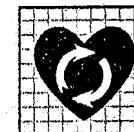
Each flavored chewable contains 272 mcg ivermectin  
and 227 mg pyrantel as pamoate salt.

# IVERHART™ PLUS

(ivermectin/pyrantel)

**Flavored Chewables**

**51 to 100 lbs**



Store at controlled room temperature of  
59°– 86°F (15°– 30°C).

Protect product from light

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Lot & Exp

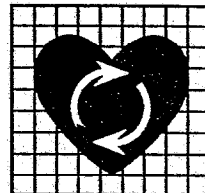
Product Code XXXXXX-01

**virbac**

# IVERHART™ PLUS.

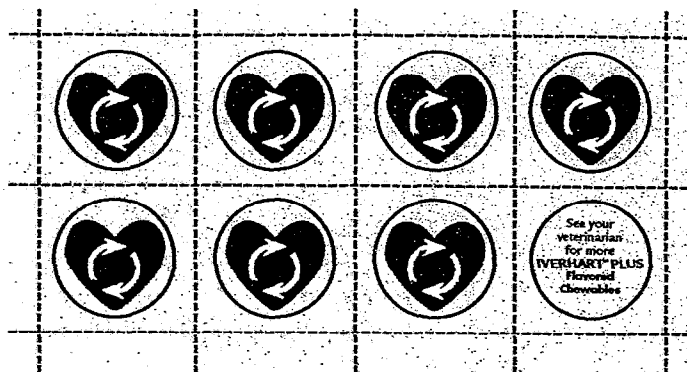
(ivermectin/pyrantel)

ANADA 200-302



Administer once a month to prevent heartworm disease and to treat and control ascarid and hookworm infections in dogs.

**virbac**



**Pink dashed line indicates where individual reminder stickers will be perforated to facilitate the dispensing of the appropriate number of stickers for the number of tablets dispensed.**





08823111

# Heartgard® Plus

(ivermectin/pyrantel)

8823111

## Chewables

**Caution:** Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

**INDICATIONS:** For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis*, *Toxascaris leonina*) and hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*).

**DOSAGE:** HEARTGARD® Plus should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Pyrantel Content	Color Coding on Foil Backing and Carton
Up to 25 lb	1	68 mcg	57 mg	Blue
26 to 50 lb	1	136 mcg	114 mg	Green
51 to 100 lb	1	272 mcg	227 mg	Brown

HEARTGARD Plus is recommended for dogs 6 weeks of age and older.  
For dogs over 100 lb use the appropriate combination of these chewables.

**ADMINISTRATION:** Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to its box to protect the product from light. Because most dogs find HEARTGARD Plus palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food. The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

HEARTGARD Plus should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of HEARTGARD Plus must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with HEARTGARD Plus and resumption of the recommended dosing regimen minimizes the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD Plus also provides effective treatment and control of ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*). Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

\*HEARTGARD is a registered trademark of Merial.

**EFFICACY:** HEARTGARD® Plus (ivermectin/pyrantel) Chewables, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D. immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. HEARTGARD Plus Chewables are also effective against canine ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*).

**ACCEPTABILITY:** In acceptability and field trials, HEARTGARD Plus was shown to be an acceptable oral dosage form that was consumed at first offering by the majority of dogs.

**PRECAUTIONS:** All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD Plus which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with HEARTGARD Plus.

While some microfilariae may be killed by the ivermectin in HEARTGARD Plus at the recommended dose level, HEARTGARD Plus is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children. In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store at controlled room temperature of 59°-86°F (15°-30°C). Protect product from light.

**ADVERSE REACTIONS:** In clinical field trials with HEARTGARD Plus, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of HEARTGARD: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

**SAFETY:** HEARTGARD Plus has been shown to be bioequivalent to HEARTGARD, with respect to the bioavailability of ivermectin. The dose regimens of HEARTGARD Plus and HEARTGARD are the same with regard to ivermectin (6 mcg/kg). Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. HEARTGARD demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of HEARTGARD products in dogs, including Collies, when used as recommended.

HEARTGARD Plus has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with HEARTGARD Plus in a heartworm disease preventive program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

**HOW SUPPLIED:** HEARTGARD Plus is available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6, 9, and 12 chewables.



Merial Limited  
2100 Ronson Road  
Iselin, New Jersey 08830-3077, U.S.A.

(Merial Limited: Registered in England and Wales [Reg. No. 3332751] with registered offices at 27 Knightsbridge, London, SW1X 7QT, England and domesticated in Delaware, USA as Merial LLC).

U.S. Pat. 4,199,569  
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January 1998